REMARKS

Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending and are still pending and under examination in this application. No new matter has been added.

Rejections Under 35 U.S.C. §112

The Examiner maintained the rejection of claims 1, 6, 11, 16, and 71-74 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner maintains that there is no support in the originally filed claims or specification for the phrase "one or more" diabetic complications. The Examiner concedes that the specification on page 6, lines 18-19, provides support for "one" diabetic complication but asserts that the support for "or more" complications on page 3 is "disclosed in the context of evaluating the likelihood that an individual will benefit from treatment and not in the context of characterizing a risk profile for developing diabetes as claimed."

The specification provides support for the phrase "or more" (than one) diabetic complications "in the context of characterizing a risk profile for developing diabetes" on page 4 lines 33-34 which recites (emphasis added):

> "According to another aspect of the invention, a method is provided for characterizing an individual's risk profile of developing future diabetes or diabetic complications."

Support for "or more" (than one) diabetic complications is also found in claim 1 as filed. Claim 1 as filed recites (emphasis added):

"1. A method for characterizing an apparently healthy individual's risk profile of developing future diabetes or diabetic complications, comprising:

obtaining a level of a marker of systemic inflammation in the individual,

comparing the level of the marker to a predetermined value specific for the diagnosis of diabetes or diabetic complications, and

characterizing the individual's risk profile of developing a future diabetes based upon the level of the marker in comparison to the predetermined value."

Thus, the specification provides support for the phrase "one or more" diabetic complications. In view of the above arguments and amendments, withdrawal of the claim rejections under 35 U.S.C. 112, first paragraph is kindly requested.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view Rodriguez-Moran et al. (Journal of Diabetes and Its Complications 13;4:211-215, 1999) The Examiner states that Rodriguez-Moran teaches that elevated serum CRP levels have been found in type II diabetics and in diabetics with foot ulcers and that elevated serum CRP levels are also found in noncontrolled type II diabetic patients. The Examiner asserts that "[wh]ile the reference does not specifically teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for said uses given CRP's known association with type II diabetes, i.e., it is obvious to measure a known marker for the presence of, or predisposition to a disease."

Applicant respectfully traverses the rejection. The instant claims are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations.

Rodriguez-Moran does not, and could not, address whether a level of CRP is predictive of developing diabetes (or one or more diabetic complications) or whether an apparently healthy individual (i.e., without diabetes) would benefit from prophylactic treatment to prevent diabetes or one or more diabetic complications. Rodriguez-Moran did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Rodriguez-Moran compared the serum levels of CRP in type II diabetic patients (i.e., after the diabetic disorder happened). Rodriguez-Moran teaches that patients with type II diabetes had significantly higher serum levels of CRP. Rodriguez-Moran is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing diabetes in the future.

It should be noted that the study of Rodriguez-Moran was not designed in a manner that would permit one to conclude that elevated levels of CRP predict diabetes. The Rodriguez-Moran study only shows that patients with diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the data in Rodriguez-Moran, one of ordinary skill in the art would have known that it is impossible to conclude definitively that the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes. In fact, the teachings of Rodriguez-Moran suggest that elevated

CRP (a known marker of inflammation) is more likely the result of the diabetic condition rather than the cause of the diabetes (see Rodriguez-Moran p. 215 right-hand column):

> "A probable involved pathway could be related to the raising of serum viscosity and shear stress associated to hyperglycemia, producing endothelium dysfunction and inflammation and in this way, increasing citokines release and thus elevating CRP levels."

Thus, Rodriguez-Moran does not address whether the level of CRP is *predictive* of diabetes in *apparently healthy* individuals.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Rodriguez-Moran et al. is respectfully requested.

The Examiner rejected claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Schalkwijk et al. (Diabetologica (1999) 42:351-357). The Examiner states that Schalkwijk teaches that elevated serum CRP levels have been found in type I diabetes particularly referring to the Results on page 211 and to table 2. The Examiner asserts that "[wh]ile the reference does not specifically teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for said uses given CRP's known association with type I diabetes, i.e., it is obvious to measure a known marker for the presence of, or predisposition to a disease."

Applicant respectfully traverses the rejection. The arguments presented above in response to the rejection of the claims as obvious in view Rodriguez-Moran are reiterated here. As stated above, the instant claims all are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations.

Schalkwijk does not, and could not, address whether a level of CRP is predictive of developing diabetes (or one or more diabetic complications) or whether an apparently healthy individual (i.e., without diabetes) would benefit from prophylactic treatment to prevent diabetes or one or more diabetic complications. Schalkwijk did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Schalkwijk compared the serum levels of CRP in type I diabetic patients (i.e., after the diabetic disorder happened). Schalkwijk teaches

that patients with type I diabetes had significantly higher serum levels of CRP. Schalkwijk is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing diabetes in the future. It should be noted that the study of Schalkwijk was not designed in a manner that would permit one to conclude that elevated levels of CRP predict diabetes. The Schalkwijk study only shows that patients with diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the data in Schalkwijk, one of ordinary skill in the art would have known that it is impossible to conclude definitively that the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes. In fact, the teachings of Schalkwijk suggest that elevated CRP is more likely the result of the diabetic condition rather than the cause of the diabetes (see Schalkwijk p. 356):

> "Various possible mechanisms could induce chronic low degree inflammation in diabetes, including activation of macrophages, increased oxidative stress or an induction of cytokines. One of the pathophysiological consequences of hyperglycaemia is the phenomenon of nonenzymatic glycation and the formation of advanced glycation end products (AGEs). AGEs have been shown to activate macrophages, to increase oxidative stress and to induce, in macrophages, the synthesis of interleukin-1 and tumor necrosis factor-α and, in vivo in mice, the expression of interleukin-6 mRNA. Many of the possible mechanisms leading to chronic low degree inflammation could be related to nonenzymatic glycation. Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." (Citations omitted)

Thus, Schalkwijk does not address whether the level of CRP is *predictive* of diabetes in *apparently healthy* individuals.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious in view of Schalkwijk is respectfully requested.

Conclusion

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Ridker et al., Applicant

By: _____

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